a patient with myelodysplastic syndrome and acute myeloid leukemia evolving from polycythemia vera (PV) treated with hydroxyurea for 4 years.

A 43-year-old man presented with facial erythrosis and intense itching in June 1991. Physical examination revealed splenomegaly. Complete blood count revealed a red blood count of 8.4×10^{12}/l, hemoglobin of 24 g/dl, hematocrit of 72.1%, white blood count (WBC) of 18×10^9/l, and a platelet count of 218×10^9/l. According to standard criteria the diagnosis of PV was made. In an attempt to promptly restore a normal red-cell mass, phlebotomy was performed. Four months later, the platelet count rose above 600×10^9/l, and the patient was then treated with hydroxyurea. The patient received between 1,000–2,000 mg/day with excellent control of blood counts. After 4 years of therapy with hydroxyurea he developed pancytopenia. The dose of hydroxyurea was decreased but the cell counts worsened and he developed bone pain, asthenia, and splenomegaly. The hydroxyurea was stopped, and a bone-marrow examination was performed, revealing massive trilineage hyperplasia with marked cytologic abnormalities, 27% of ringed sideroblasts, and a 20% increase of immature myeloid forms. Cytogenetic analysis revealed −1, −5, −9, −17, 7p+, 12p+, del(17)(q23). Ten days later the WBC rose to 81×10^9/l. Bone-marrow examination was repeated and revealed acute myeloid leukemia, FAB type M5. He was induced with doxorubicin and cytosine arabinoside (3 + 7 regimen), but he failed to respond and died from intraalveolar hemorrhage, sepsis, and leukostasis.

Patients with PV, especially if they have been treated with alkylating agents or radioactive phosphorus, are at an increased risk of developing acute leukemia [2]. Therefore it could be argued that the acute leukemia we observed reflects the natural course of PV rather than a hydroxyurea-related mutagenic effect. However, the presence of cytogenetic abnormalities and of a myelodysplastic phase preceding the development of frank leukemia argues for a therapy-related leukemia. Indeed, a close correlation between previous cytotoxic therapy, presence of a myelodysplastic phase, and abnormalities of chromosomes 5 and 7 has been reported [3]. The leukemogenicity of hydroxyurea has been evoked in 3 cases of acute myeloid leukemia evolving from 30 patients with PV treated with hydroxyurea alone [4].

This case further supports the view that hydroxyurea may have leukemogenic effects, and emphasizes the need for collecting data on malignancies occurring after long-term treatment before any conclusion can be drawn on the safety of hydroxyurea long-term treatment.

Marc Pulik
François Lionnet
Philippe Genet
Charlotte Petitdidier
Laure Jary
Tahar Touahri

Department of Hematology, Argenteuil, France

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Cerebellar Toxicity With Medium-Dose Cytarabine in a Young Patient With Renal Insufficiency

To the Editor: Cytosine arabinoside (Ara-C) is an antimetabolite and is efficacious at conventional doses (100–200 mg/m^2) in both acute myeloid and lymphoid leukemias. High-dose Ara-C (2–3 g/m^2) was found to be useful in salvage therapy of relapsed and refractory acute leukemia [1], as well as in improving disease-free survival when used as consolidation in AML [2]. However, acute cerebellar toxicity, due to damage of Purkinje cells [3], was found to be a dose-limiting side effect, with frequency of cerebellar dysfunction increasing rapidly after a cumulative dose of 36 g/m^2. Age was identified as the most important risk factor [4]. Cerebellar dysfunction has been rarely reported to occur in lower doses of Ara-C in young patients.

A 40-year-old woman with systemic lupus erythematosus and lupus nephritis presented with pancytopenia, and marrow examination confirmed the diagnosis of acute myeloid leukemia. She had no signs and symptoms of active lupus disease. Laboratory tests showed impaired renal function (urea, 30 mmol/l; creatinine, 285 mmol/l) with normal liver function. Serological tests showed anti-DNA of 160 I.U., normal complement level, and normal sedimentation rate. Induction chemotherapy consisting of cytarabine infusion (100 mg/m^2/day × 7 days) with daunorubicin (50 mg/m^2/day × 3 days) was given. Reassessment bone marrow showed nonremission, and she was reinduced with medium-dose cytarabine (500 mg/m^2 twice daily × 4 days) and mitoxantrone (12 mg/m^2 daily × 3 days). She developed sudden onset of mental deterioration, unsteadiness, and slurring of speech on the fourth day of cytarabine infusion. Physical examination revealed gross truncal ataxia, nystamus, intentional tremor, and dysdiadochokinesis. Electrolytes were normal, and there was no evidence of active lupus disease. Urgent computed tomography of the brain did not reveal any abnormality. Magnetic resonance imaging of the brain was also normal. Ara-C was stopped and she gradually improved, with minimal signs of cerebellar dysfunction detected after a week.

Ara-C is mainly metabolized in the liver by deamination, so that dose reduction is not usually necessary in patients with impaired renal function. In our case, the cerebellar toxicity was unlikely to be due to cumulative toxicity, as the dose of Ara-C given was low (3.7 g/m^2). The only risk factor identifiable was impaired renal function. However, acute cerebellar toxicity had been noted in patients with impaired renal function when higher doses (infusion of 2–3 g/m^2) of Ara-C were administered [5]. This case therefore illustrates that neurological toxicity may develop even in young patients at lower doses of Ara-C in renal insufficiency, underscoring the importance of careful monitoring of patients with impaired renal function who are receiving Ara-C of higher than conventional doses. Immediate cessation of Ara-C on development of signs of cerebellar toxicity is compatible with full neurological recovery.

C.S. Chim
Y.L. Kwong

Department of Medicine, Queen Mary Hospital, Hong Kong

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